ORAL DRUG DELIVERY – MOLECULAR DESIGN AND TRANSPORT MODELING

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VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

ABSTRACT

Pharmacokinetic Modeling of Oral Drug Delivery

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One of the major challenges faced by the pharmaceutical industry is to accelerate the product innovation process and reduce the time-to-market for new drug developments. This involves billions of dollars of investment due to the large amount of experimentation and validation processes involved. A computational modeling approach, which could explore the design space rapidly, reduce uncertainty and make better, faster and safer decisions, fits into the overall goal and complements the product development process. Our research focuses on the early preclinical stage of the drug development process involving lead selection, optimization and candidate identification steps. Our work helps in screening the most favorable candidates based on the biopharmaceutical and pharmacokinetic properties. This helps in precipitating early development failures in the early drug discovery and candidate selection processes and reduces the rate of late-stage failures, which is more expensive.

In our research, we successfully integrated two well-known models, namely the drug release model (dissolution model) with a drug transport model (compartmental absorption and transit (CAT) model) to predict the release, distribution, absorption and elimination of an oral drug through the gastrointestinal (GI) tract of the human body. In the CAT model, the GI tract is envisioned as a series of compartments, where each compartment is assumed to be a continuous stirred tank reactor (CSTR). We coupled the drug release model in the form of partial differential equations (PDE's) with the CAT model in the form of ordinary differential equations (ODE's). The developed model can also be used to design the drug tablet for target pharmacokinetic characteristics. The advantage of the suggested approach is that it includes the mechanism of drug release and also the properties of the polymer carrier into the model. The model is flexible and can

be adapted based on the requirements of the clients. Through this model, we were also able to avoid depending on commercially available software which are very expensive.

In the drug discovery and development process, the tablet formulation (oral drug delivery) is an important step. The tablet consists of active pharmaceutical ingredient (API), excipients and polymer. A controlled release of drug from this tablet usually involves swelling of the polymer, forming a gel layer and diffusion of drug through the gel layer into the body. The polymer is mainly responsible for controlling the release rate (of the drug from the tablet), which would lead to a desired therapeutic effect on the body.

In our research, we also developed a molecular design strategy for generating molecular structures of polymer candidates with desired properties. Structure-property relationships and group contributions are used to estimate the polymer properties based on the polymer molecular structure, along with a computer aided technique to generate molecular structures of polymers having desired properties. In greater detail, we utilized group contribution models to estimate several desired polymer properties such as grass transition temperature (T_g), density (ρ) and linear expansion coefficient (α). We subsequently solved an optimization model, which generated molecular structures of polymers with desired property values. Some examples of new polymer repeat units are $-\left[CONHCH_2-CH_2NHCO\right]_n-$, $-\left[CHOH-COO\right]_n-$. These repeat-units could potentially lead to novel polymers with interesting characteristics; a polymer chemist could further investigate these. We recognize the need to develop group contribution models for other polymer properties such as porosity of the polymer and diffusion coefficients of water and drug in the polymer, which are not currently available in literature.

The geometric characteristics and the make-up of the drug tablet have a large impact on the drug release profile in the GI tract. We are exploring the concept of tablet customization, namely designing the dosage form of the tablet based on a desired release profile. We proposed tablet configurations which could lead to desired release profiles such as constant or zero-order release, Gaussian release and pulsatile release. We expect our work to aid in the product innovation process.

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